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# CHEMICAL EXAMINATION OF ELATERIUM AND THE CHARACTERS OF ELATERIN.\*

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The product known as "elaterium" is recognised under this title by the British Pharmacopœia (1898), and is there defined as "a sediment from the juice of the fruit of *Ecballium Elaterium*, A. Richard." The action of elaterium, which is that of a powerful hydragogue cathartic, has been ascribed to a crystalline principle, designated elaterin, which is likewise recognised by the British Pharmacopœia. In this work the specific statement is made that "elaterin,  $C_{20}H_{28}O_5$ , is the active principle of elaterium." The only other national Pharmacopœia which has given official recognition to elaterin is that of the United States of America, which defines it as "a neutral principle obtained from elaterium," possessing the formula  $C_{20}H_{28}O_5$ . It was adopted by the last-mentioned authority in 1880, to the exclusion of elaterium, and has been retained in the two succeeding revisions to the present time.

Elaterium appears never to have been subjected to a complete chemical examination, and the only constituent of it which has hitherto received consideration is the above-mentioned elaterin, of which the British Pharmacopœia requires that elaterium should yield not less than 20 per cent. In addition to elaterin, Walz,<sup>1</sup> many years ago, stated to have found in the juice of the fruits and herb of *Ecballium* four other substances, which he designated respectively as prophenin,  $C_{20}H_{36}O_7$ , ecbalin or elateric acid,  $C_{20}H_{34}O_4$ , hydro-elaterin,  $C_{20}H_{30}O_6$ , and elateride,  $C_{20}H_{32}O_{12}$ . Inasmuch as these last-mentioned products were only obtained in an amorphous or resinous state, no one of them can be regarded as representing a definite or homogeneous substance.

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<sup>1</sup> *N. Jahrb. Pharm.*, 1859, **11**, 21, 178.

The principle which occurs in commerce under the name of elaterin, and which, as above noted, is recognised under that title by the British and United States Pharmacopœias, has received the attention of several investigators during the past few years. The formula adopted for it by the Pharmacopœias, namely,  $C_{20}H_{28}O_5$ , is that first suggested by Zwenger.<sup>2</sup> Berg<sup>3</sup> has assigned to elaterin the formula  $C_{28}H_{38}O_7$ , and considers it to exist in the juice of the fruits of *Ecballium* in the form of a glucoside, which is accompanied by an enzyme designated as elaterase. The product regarded as a glucoside does not appear, however, to have been specially characterised, and was in fact only obtained in an amorphous state. Thoms,<sup>4</sup> in a report on experiments conducted by Mann, considers elaterin to possess the formula  $C_{22}H_{30}O_6$ , whereas Pollak<sup>5</sup> obtained results which were in fairly close agreement with the formula suggested by Zwenger, namely,  $C_{20}H_{28}O_5$ . Hemmelmayr,<sup>6</sup> on the other hand, with consideration of his analyses and molecular weight determinations, has assigned to elaterin the formula  $C_{24}H_{34}O_6$ . In view of the varying results of the above-mentioned investigators, it is evident that even the empirical formula of the product known as elaterin cannot as yet be considered definitely established.

The present authors, having recently had occasion to prepare some elaterin, have deemed it of interest to examine the other constituents of elaterium, so far as the limited quantity of material available would permit. At the same time some commercial specimens of elaterin have been examined, and the very interesting and important facts which have thus been revealed, together with the deductions therefrom, are summarised at the end of this paper.

#### EXPERIMENTAL.

The material employed for this investigation consisted of the best English elaterium, which was obtained from a reliable source, and conformed in its general characters to the requirements of the British Pharmacopœia.

Determinations of the amount of moisture and of ash gave the following results:—0.4180, when heated at 110° C., lost

<sup>2</sup> *Ann. d. Chem.*, 1842, **43**, 460.

<sup>3</sup> *Bull. Soc. Chim.*, 1897 [iii.], **17**, 85, and 1906 [iii.], **35**, 435; *Chem. Centralblatt*, 1897, I., 483, and 1906, II., 610; *Pharm. Journ.*, 1906, **77**, 283; *Compt. rend.*, 1907, **143**, 1161, and *Chem. Centralblatt*, 1907, I., 636; *Compt. rend.*, 1909, **148**, 566, and *Chem. Centralblatt*, 1909, I., 1239.

<sup>4</sup> *Chem. Zeit.*, 1906, p. 923, and *Pharm. Journ.*, 1906, **77**, 351.

<sup>5</sup> *Ber. d. deutsch. chem. Ges.*, 1906, **39**, 3380.

<sup>6</sup> *Ibidem*, 1906, **39**, 3652.

0.0220  $\text{H}_2\text{O}$ .  $\text{H}_2\text{O}$  = 5.3 per cent. 0.5015 left on ignition 0.0335 of ash. or 6.7 per cent.

For the purpose of a complete examination a quantity (25 grammes) of the finely powdered elaterium was suspended in 500 C.c. of water, and a current of steam passed through the mixture for about an hour. The distillate was neutral to litmus, and, apart from a minute quantity of solid particles, was free from volatile substances.

After the distillation with steam, there remained in the flask an almost colourless, aqueous liquid, which may be designated as (A), together with some insoluble material (B). When cold, the latter was separated by filtration and repeatedly washed with cold water, the washings being added to the aqueous liquid.

*Examination of the Aqueous Liquid (A).*

The above-mentioned aqueous liquid was concentrated under diminished pressure to a volume of 250 C.c., when it remained nearly colourless, and possessed a slightly bitter taste. It reduced Fehling's solution very slowly, and did not respond to the usual tests for alkaloids. With iodine it gave a distinct reaction for starch, although the amount of the latter present was evidently very small. The liquid was repeatedly shaken with ether and chloroform successively, but these solvents removed only traces of amorphous products. On subsequently evaporating the aqueous liquid to dryness on the water-bath, 1.5 grammes of a brown, amorphous extract were obtained. About 1.0 gramme of this material was boiled for two hours with a little water containing 5 per cent. of its weight of sulphuric acid, after which the acid was removed by baryta, and the filtered liquid concentrated. It was found to contain sugar, since it readily reduced Fehling's solution, and yielded 0.1 gramme of *d*-phenylglucosazone, melting at  $208^{\circ}$ - $210^{\circ}$ . As a small amount of dextrose would have been produced under the above conditions by the hydrolysis of the starch contained in the liquid, it cannot be concluded that any indication has thus been afforded of the presence of a glucoside.

The aqueous liquid, when administered to a dog in an amount corresponding to about 2 grammes of elaterium, had no purgative action.

*Examination of the Material Insoluble in Water (B).*

The material insoluble in water formed a grey, amorphous powder, and, after drying in a water-oven, amounted to 21



grammes. This was extracted repeatedly in a Soxhlet apparatus, first with boiling chloroform and then with hot alcohol, when a portion of the material (9 grammes) remained undissolved in the form of a brown, amorphous powder. The latter, when heated with caustic alkali, developed ammonia. It, therefore, appeared to contain some protein products, and inorganic salts were also present. When administered to a dog, in doses of 0.5 gramme, it was found to be quite inert.

The above-mentioned chloroform and alcohol extracts were united, mixed with purified sawdust, and the thoroughly dried mixture extracted successively in a Soxhlet apparatus with I. light petroleum (b.p. 35-50°); II. ether; III. chloroform; and IV. alcohol.

#### I. *Petroleum Extract.*

The extraction with petroleum was continued for about forty hours. This resulted in the removal of 1.8 grammes of material, of which 0.8 gramme was readily soluble in light petroleum, while the remainder (1.0 gramme) was sparingly soluble in that liquid.

*The readily-soluble extract* was a soft, green mass. The greater portion of it (0.6 gramme) was boiled for some hours with 5 C.c. of an alcoholic solution of potassium hydroxide, the alcohol then removed, and water added, when a small quantity of amorphous material separated. This was removed by shaking with ether, when, on evaporating the solvent, a very small amount of a colourless substance was obtained. The latter yielded the colour reactions of the phytosterols, but the amount available was much too small to permit of its further investigation.

The alkaline liquid, from which the unsaponifiable material had been removed by ether, as above described, was acidified and again extracted with ether, the ethereal liquid being washed, dried, and the solvent removed. A small quantity (0.3 gramme) of fatty acids was thus obtained, which was distilled under diminished pressure. The distillate, when cold, became partially solid, and apparently consisted of a mixture of saturated and unsaturated fatty acids.

*The sparingly-soluble extract* formed a pale green powder. This was treated with ether (2-3 C.c.), when most of it dissolved, but from the solution nothing crystalline could be obtained. The undissolved portion (0.3 gramme) could be crystallised from dilute alcohol, from which it separated in

small, colourless plates, melting indefinitely between  $170^{\circ}$ - $180^{\circ}$ .

The principal products from the petroleum extract were submitted to physiological tests by administering 0.1 gramme of each to dogs. The results were as follows :—

The readily-soluble extract caused no purgation.

The sparingly-soluble extract caused slight purgation and slight vomiting six hours after administration.

The crystalline substance (m.p.  $170^{\circ}$ - $180^{\circ}$ ) obtained from the last-mentioned extract caused slight purgation and severe vomiting five to eight hours after administration.

## II. *Ether Extract.*

The extraction with ether, as in the case of the preceding treatment with petroleum, was very prolonged, having been continued for about fifty hours. By this means 8.7 grammes of material were removed, of which 1.2 grammes were fairly soluble in ether, while the remainder (7.5 grammes) was very sparingly soluble in that liquid.

*The more readily-soluble extract* was a dark green resin. It was dissolved in ether, and the ethereal solution repeatedly shaken with aqueous sodium carbonate. By this means a small amount of an almost black, resinous product was removed, from which nothing definite could be isolated. The ethereal liquid was subsequently washed with water, dried, and the solvent removed, when a small quantity of nearly colourless material was obtained. This was crystallised from dilute alcohol, when it separated in plates, melting at about  $180^{\circ}$ - $185^{\circ}$ , but the amount of substance was too small to permit of its further investigation.

*The sparingly-soluble extract* formed a nearly colourless, tasteless, crystalline powder, melting and decomposing at  $217^{\circ}$ - $220^{\circ}$ . This product corresponds to the "elaterin" of the pharmacopœias. It is sparingly soluble in alcohol and in ether, readily soluble in chloroform, and is precipitated from its solution in the latter by the addition of ether.

By a prolonged process of fractional crystallisation from absolute alcohol, it has been possible to show that the above-described product is not homogeneous, since it may be resolved into several fractions, whose melting-points range from  $230^{\circ}$ , in the case of the most sparingly-soluble fraction, to  $190^{\circ}$ - $195^{\circ}$  in that of the most soluble one. The varying character of the fractions obtained from 6.5 grammes of

the above-mentioned crude elaterin is indicated in the following table :—

Fraction.	Quantity.	Melting Point.*	Crystalline Form.	Solubility in Alcohol.
I.	2.5 Gm.	230° C.	Hexagonal Prisms	Very sparingly soluble
II.	1.5 Gm.	228-230°	Ditto	Very sparingly soluble
III.	0.5 Gm.	203-207°	Prisms	Sparingly soluble
IV.	0.4 Gm.	198-202°	Ditto	More soluble than the preceding
V.	0.4 Gm.	190-195°	Plates	Readily soluble

Analyses of the crude elaterin (m.p. 217°-220°), and of fractions I. and V. obtained therefrom gave the following results :—

*Crude Elaterin* (m.p. 217°-220°).—0.1264 gave 0.3204 CO<sub>2</sub> and 0.0918 H<sub>2</sub>O. C = 69.1; H = 8.1 per cent.

*Fraction I.* (m.p. 230°).—0.1236 gave 0.3122 CO<sub>2</sub> and 0.0885 H<sub>2</sub>O. C = 68.9; H = 7.9 per cent.

*Fraction V.* (m.p. 190°-195°).—0.1396 gave 0.3530 CO<sub>2</sub> and 0.1030 H<sub>2</sub>O. C = 68.9; H = 8.2 per cent.

The various empirical formulæ which have hitherto been assigned to elaterin require the following percentages of carbon and hydrogen :—

C<sub>20</sub>H<sub>28</sub>O<sub>5</sub>. M.W.=348 (Zwenger) requires C=68.9; H=8.0%  
 C<sub>24</sub>H<sub>34</sub>O<sub>6</sub>. M.W.=418 (Hemmelmayer) ,, C=68.9; H=8.0%  
 C<sub>28</sub>H<sub>38</sub>O<sub>7</sub>. M.W.=486 (Berg) ,, C=69.1; H=7.8%  
 C<sub>22</sub>H<sub>30</sub>O<sub>6</sub>. M.W.=390 (Thoms) ,, C=67.7; H=7.7%

A molecular weight determination was made of the fraction of elaterin melting at 230°, by means of the ebullioscopic method, and with the use of chloroform as the solvent. 0.6895 gramme of the substance in 37.3 grammes of chloroform gave

$$\Delta t + 0.148^{\circ}, \text{ whence M.W.} = 457.$$

It will be seen from the results of the above analyses that a crude elaterin and the fractions therefrom which represent the extremes of solubility and melting point agree very closely in their percentage composition. Notwithstanding this fact, they exhibited very marked differences in their specific rotatory power and in their physiological action, as indicated below :—

*Crude Elaterin* (m.p. 217—220°).—0.2035 in 20 C.c. of chloroform gave  $\alpha_D - 0^{\circ} 20'$  in a 2 dm. tube, whence  $[\alpha]_D - 16.4^{\circ}$ .

\* The fusion of these products is attended with decomposition.



*Fraction I.* (m.p.  $230^{\circ}$ ).—0.1416 in 20 C.c. of chloroform gave  $a_D -0^{\circ} 45'$  in a 2 dm. tube, whence  $[\alpha]_D -52.9^{\circ}$ .

*Fraction III.* (m.p.  $203-207^{\circ}$ ).—0.2060 in 20 C.c. of chloroform gave  $a_D -0^{\circ} 11'$  in a 2 dm. tube, whence  $[\alpha]_D -8.9^{\circ}$ .

*Fractions IV. and V. United* (m.p.  $190-202^{\circ}$ ).—0.1200 in 20 C.c. of chloroform gave  $a_D + 0^{\circ} 10'$  in a 2 dm. tube, whence  $[\alpha]_D + 13.9^{\circ}$ .

The physiological action of the crude elaterin and the various fractions obtained therefrom were determined by the administration of 0.1 gramme in each case to dogs.

*Crude Elaterin* produced purgation.

*Fraction I.* (m.p.  $230^{\circ}$ ) had no effect.

*Fraction II.* (m.p.  $228-230^{\circ}$ ) had no effect.

*Fraction III.* (m.p.  $203-207^{\circ}$ ) produced repeated, but not violent purgation.

*Fraction IV.* (m.p.  $198-202^{\circ}$ ) produced purgation, and was more drastic than *Fraction III.*, but its action was not violent, and no vomiting occurred.

*Fraction V.* (m.p.  $190-195^{\circ}$ ) produced very severe purgation, accompanied by repeated vomiting. The motions contained much epithelium and mucus, and the animal was very unwell for two days.

It will be apparent from the above results that by the fractional crystallisation of 6.5 grammes of crude elaterin it was possible to separate 4 grammes, or 61 per cent., of a substance which, in doses of 0.1 gramme, was completely devoid of purgative properties. It will also be observed that the degree of physiological activity exhibited by these products appears to be dependent upon the proportion of the dextro-rotatory compound present; for while the above-described crude elaterin, having  $[\alpha]_D -16.4^{\circ}$ , produced some purgation, the principal fraction (I.), which was much more strongly lævo-rotatory ( $[\alpha]_D -52.9^{\circ}$ ), was quite devoid of this property. On the other hand, the highest degree of physiological activity was shown by the two most-readily soluble fractions, which together were dextro-rotatory, having  $[\alpha]_D + 13.9^{\circ}$ .

In view of the facts above noted, it was deemed desirable to ascertain the character of commercial elaterin. For this purpose two representative samples were obtained, one of which was guaranteed to be of English manufacture, while the other was of German origin.

*English Elaterin.*—This was a white, crystalline product, which corresponded in its general characters to the descrip-

tion given of elaterin in the British Pharmacopœia. It melted at 230—231°. A determination of its specific rotatory power gave the following result.

0·2040 in 20 C.c. of chloroform gave  $\alpha_D - 0^\circ 58'$  in a 2 dcm. tube, whence  $[\alpha]_D - 47\cdot8^\circ$ .

It was subjected to one crystallisation from absolute alcohol, when a principal fraction was obtained which melted at 231-232°, and constituted about 75-80 per cent. of the whole. This product may be designated as Fraction I., and the remainder of the material, obtained by the evaporation of the mother-liquors, as Fraction II.

*Fraction I.* (m.p. 231-232°).—0·2030 in 20 C.c. of chloroform gave  $\alpha_D - 1^\circ 2'$  in a 2 dcm. tube, whence  $[\alpha]_D - 50\cdot9^\circ$ .

*Fraction II.*—0·1170 in 20 C.c. of chloroform gave  $\alpha_D - 0^\circ 15'$  in a 2 dcm. tube, whence  $[\alpha]_D - 21\cdot3^\circ$ .

This specimen of English elaterin and the fractions obtained therefrom were submitted to physiological tests, with the following results:—

The original elaterin, when administered in an amount of 0·1 gramme to a dog, produced purgation.

*Fraction I.*, when given in amounts of 0·1 gramme, produced no effect, even after twenty-four hours. In doses of 0·005 gramme it also had no effect on man.

*Fraction II.*, in an amount of 0·07 gramme, produced well-marked purgation.

*German Elaterin.*—This was a white crystalline powder, similar in appearance to the above-described English product. It melted at 223°. A determination of its specific rotatory power gave the following result:—

0·2000 in 20 C.c. of chloroform gave  $\alpha_D - 0^\circ 39'$  in a 2 dcm. tube, whence  $[\alpha]_D - 32\cdot5^\circ$ .

It was twice recrystallised from absolute alcohol, when a product was obtained which melted at 229-231°, and constituted about 60 per cent. of the whole. This product may be designated as Fraction I., and the remainder of the material, obtained by the evaporation of the mother-liquors, as Fraction II.

*Fraction I.* (m.p. 229-231°).—0·2025 in 20 C.c. of chloroform gave  $\alpha_D - 1^\circ 1'$  in a 2 dcm. tube, whence  $[\alpha]_D - 50\cdot2^\circ$ .

*Fraction II.*—0·1720 in 20 C.c. of chloroform gave  $\alpha_D + 0^\circ 15'$  in a 2 dcm. tube, whence  $[\alpha]_D + 14\cdot5^\circ$ .

This specimen of German elaterin and the principal fraction (I.) obtained therefrom were submitted to physiological tests, with the following results.

The original elaterin, when administered to a dog in an amount of 0.05 gramme, had a distinct purgative action, whereas Fraction I., when given in the same amount, had no effect.

The above-described results are thus in complete accordance with those obtained from the elaterin prepared by ourselves from the best English elaterium. They afford conclusive evidence that the elaterin supplied by both English and German manufacturers consists to a large extent of a substance devoid of purgative properties, and which may be separated by a simple process of fractional crystallisation. In the two specimens above referred to, that of English manufacture appears to have been somewhat further purified than the German, and, therefore, contained a relatively larger proportion of the inactive constituent.

### III. and IV. *Chloroform and Alcohol Extracts.*

These extracts amounted to 0.2 and 0.3 gramme respectively. They consisted of brown, resinous material, from which nothing definite could be isolated. Both of them were found to produce purgation when administered to dogs in doses of 0.1 gramme, but this was probably due to the presence of small amounts of active substance which had escaped extraction by the preceding treatment with ether.

### SUMMARY AND CONCLUSIONS.

The results of the present investigation, and the conclusions to be drawn from them, may be summarised as follow:—

The material employed consisted of the best English elaterium, which contained 5.3 per cent. of moisture, and yielded 6.7 per cent. of ash.

The proportion of the elaterium which was soluble in water corresponded to about 6 per cent. of its weight. The aqueous liquid contained a very small amount of starch, the presence of which was confirmed in another authentic specimen of the drug. The requirement of the British Pharmacopœia, which is possibly based on the observations recorded in 'Pharmacographia' (second edition, p. 294), that elaterium "should not give the characteristic reactions with the tests for starch," is therefore not valid. The statement in the Phar-

macopœia of 1885 that elaterium "boiled with water and the cooled mixture treated with iodine affords little or no blue colour," more correctly expresses the facts, for the amount of starch may be so small as to become completely hydrolysed by prolonged boiling with water. The aqueous liquid, when evaporated to dryness, yielded a brown, amorphous mass which was quite devoid of purgative properties.

The portion of elaterium which was insoluble in water amounted, when dried, to 84 per cent. of its weight. On extracting this material successively with hot chloroform and alcohol 57 per cent. of it was dissolved. The portion which was not removed by these solvents consisted of inert material containing some inorganic salt.

The combined chloroform and alcohol extracts of the portion of elaterium which was insoluble in water were extracted successively with light petroleum, ether, chloroform, and alcohol.

*The petroleum extract*, which amounted to about 15 per cent. of the whole, contained a very small amount of a colourless, crystalline substance, melting indefinitely between 170° and 180°. After hydrolysis with alcoholic potassium hydroxide the extract yielded a mixture of fatty acids, together with a very small amount of a substance giving the colour reactions of the phytosterols.

*The ether extract* amounted to about 73 per cent. of the whole. The larger proportion of this extract (about 86 per cent.) consisted of a nearly colourless, crystalline product, melting and decomposing at 217-220°. This product corresponds to the "elaterin" of the Pharmacopœias, and the yield represents 30 per cent. of the elaterium originally employed.

*The chloroform and alcohol extracts* amounted to only 1.7 and 2.5 per cent. respectively of the whole, and consisted of brown resins.

The most important product obtained from elaterium is that officially recognised as *elaterin*, and special consideration has therefore been given to the character of this product in the present investigation.

It is well known that elaterium, even when most carefully prepared, is subject to considerable variation, especially with regard to its physiological activity. This fact received consideration in the 'Pharmacographia,' where (second edition, p. 295) the following comments were recorded:—"Elaterin is



not employed in medicine, but seeing how much elaterium is liable to vary from climate or season it might probably be introduced into use with advantage." It is possibly in consequence of this suggestion that elaterin was introduced into the British Pharmacopœia in 1885, and that, since 1880, it has been recognised by the United States Pharmacopœia.

The introduction of elaterin as a medicinal agent was evidently based on the assumption that it is a homogeneous substance, representing the active principle of elaterium, and it is, in fact, defined or described as such by the Pharmacopœias. In accordance with this view, a method for the valuation of elaterium has been proposed, which consists in determining the amount of "elaterin" which it yields on extracting with chloroform and purifying the residue left on the evaporation of this solvent by treatment with ether (compare 'Year-Book of Pharmacy,' 1886, p. 442).

The results of the present investigation have quite conclusively shown that the product known as "elaterin" is not a homogeneous substance, but that as prepared by ourselves from the best English elaterium, or as supplied by English and German manufacturers, it contains from 60 to 80 per cent. of a colourless, crystalline substance which is completely devoid of purgative action, when administered to dogs in amounts of 0.1 gramme, or to man in doses of 0.005 gramme. This substance melts and decomposes at about  $230^{\circ}$ , and is *levo*-rotatory, the highest specific rotation thus far observed having been  $[\alpha]_D - 52.9^{\circ}$ . It is accompanied in the crude elaterin by varying amounts of a crystalline compound of apparently the same empirical composition, but which possesses a very high degree of physiological activity. The last-mentioned compound has not as yet been obtained in a state of purity, owing to the relatively small proportion of it present in crude elaterin. It is, however, *dextro*-rotatory, a product possessing  $[\alpha]_D + 13.9^{\circ}$  having been obtained.

A comparison of the physiological action of crude elaterin and that of the various fractions obtained therefrom with respect to their specific rotatory power, has rendered it evident that the purgative action is dependent upon the proportion of *dextro*-rotatory substance present. By the ordinary process of purification, therefore, such as repeated crystallisation, the amount of active substance in "elaterin" becomes diminished, or it may even be completely removed. The appreciable differences in composition and activity which have been observed in the specimens of English and German



elaterin now examined may thus be attributed to the varying degrees of purification to which they have been subjected.

With consideration of the results above noted, it is evident that the product designated as "elaterin," and officially recognised under that title, is so variable in character as to require the adoption of some standard of physiological activity before it can be considered suitable for medicinal use. If it were deemed desirable that such a product should be retained in the Pharmacopœia, the only means, apparently, whereby its approximate uniformity could be ensured and controlled would be by the adoption of definite limits for its specific optical rotation. The dosage of a product conforming to such a standard could then be adjusted in accordance with the results obtained by physiological or clinical tests.

An investigation of the constituents of the entire fresh fruits of *Ecballium Elaterium* is now in progress, the material for which has kindly been supplied to us by Messrs. W. Ransom and Son, of Hitchin.

In conclusion, we desire to express our best thanks to Dr. H. H. Dale, Director of the Wellcome Physiological Research Laboratories, and to his associate Dr. P. P. Laidlaw, for conducting the physiological tests which the present investigation has involved.